SUMMARY MINUTES

OF THE

CIRCULATORY SYSTEM DEVICES PANEL MEETING

JULY 21-22,1998

Holiday Inn Gaithersburg, Ballroom
Two Montgomery Village Avenue
Gaithersburg, MD

CIRCULATORY SYSTEM DEVICES PANEL MEETING

July21, 1998

PANEL PARTICIPANTS

ACTING CHAIRPERSON

Tony W. Simmons, M.D.

EXECUTIVE SECRETARY

John E. Stuhlmuller, M.D.

VOTING MEMBERS

Michael D. Crittenden, M.D.

CONSULTANTS APPOINTED TO TEMPORARY VOTING STATUS

Salim Aziz, M.D.

Jeffery A. Brinker, M.D.

Cynthia M. Tracy, M.D.

George W. Vetrovec, M.D.

INDUSTRY REPRESENTATIVE

Gary Jarvis

CONSUMER REPRESENTATIVE

Unavailable

FOOD AND DRUG ADMINISTRATION

Thomas J. Callahan, Ph.D.
Daniel Spyker, Ph. D., M.D.

Barbara Zimmerman

OPEN SESSION—

CALL TO ORDER

Tony W. Simmons, M. D., Acting Chairperson, called the meeting to order at 8:05 a.m. Executive Secretary John E. Stuhlmuller, M. D., read the conflict of interest statement. He noted that because of potential conflicts of interest, Acting Chair Dr. Simmons would participate in all discussions but not vote and that waivers had been granted to Drs. Brinker and Vetrovec allowing their full participation. He also read the appointments to temporary voting status for the four consultants to the panel.

OPEN PUBLIC HEARING

Dr. Simmons invited those present to address the panel. There were no requests to speak.

OPEN COMMITTEE DISCUSSION--PMA APPLICATION P980003

Dr. Simmons asked panel members to introduce themselves and opened discussion of PMA application P980003 for the Cardiac Pathways Corporation Cooled Ablation System.

Company Presentation

Debra Echt, M. D., described the device components and noted that the cooled catheter tip minimizes impedance rises and permits delivery of greater energy. She listed the 18 participating centers and outlined the study hypothesis, enrollment, endpoints, and design. The randomized. prospective study was stratified by frequency of ventricular tachycardia (VT), amiodarone use, and ejection fraction (EF) and used an intent-to-treat analysis. Dr. Echt described the entry criteria and study protocol and analyzed study demographics for the 75

patients who received cooled ablation and 32 control patients who received drug therapy. She noted that all patients had poor EF, numerous VT episodes, and were refractory to drug therapy.

Dr. Echt defined mappable VT and acute and long-term success and discussed VT inducibility and recurrence at six months in control and device groups. The ablation group had a 55 % long-term success rate and a 75 % acute success rate, with the latter rate similar to that in published literature on RF ablation.

Major study revisions included the elimination of randomization and of the requirement for prior drug failure. Dr. Echt described the. nonrandomized study protocol and the pooled patient data, noting that percentages for acute and long-term success for randomized and pooled patient groups were very similar. She discussed the adverse event (AE) rate and described the major and minor AEs. Dr. Echt gave survival rates for the pooled patients and the randomized study, noting an 80 % overall survival rate. She concluded that the cooled ablation system had demonstrated reduction in the clinical occurrence of VT compared to drug therapy alone, acute success rates simi lar to the published literature, and safety in patients with advanced cardiac disease and frequent, drug-refractory VT, and she read the proposed indications for use.

FDA Presentation

Barbara Zimmerman, lead FDA reviewer, thanked the review team and the sponsors. She gave the device history and compared the cooled ablation device to three market-approved cardiac ablation devices, noting the uniqueness of the cooling electrode tip. Ms. Zimmerman described the advantages and disadvantages of the closed lumen saline irrigation system and compared the specifications for RF generation for the device and other market-approved devices.

She discussed the types of preclinical testing being done, saying that results are not expected to affect clinical results.

Noting that a previous panel homework assignment had helped determine safety and effectiveness parameters, Ms. Zimmerman gave the safety results in terms of observed major and minor adverse events and stratified mortality at six-month follow-up. She listed effectiveness results in terms of acute and chronic success for the various patient cohorts. Using the randomized cohort data, she concluded that the primary endpoint of decreased recurrence of clinical VT at six months was met. On the secondary endpoints, the major adverse event rate was higher for device that than for the medical management group, but was comparable to the rate reported in published studies for VT. She noted that while there may be a higher mortality rate for those receiving ablation as compared to those receiving drug therapy, the difference was not statistically significant.

PANEL DISCUSSION

Dr. Cynthia Tracy, lead panel reviewer, raised a number of questions on technical issues, the flow of patient groups, safety and efficacy questions, and mortality data. She also asked why a comparison between standard RF and cooled ablation had not been done. Several panel members agreed that a comparison of standard RF catheters to chilled ablation or of the device using the chilled tip versus non-cooled ablation would have been useful. Dr. Tracy agreed with the FDA reviewer that cooled tip ablation may not be a low-risk system, given the high rate of adverse events but added that although the procedure is not low risk, people are willing to pay

the price. She concluded that the device does not eliminate VT or make patients live longer but does make them feel better in comparison to drug therapy.

Dr. Brinker asked whether ablation is the standard of care for stable VT, and whether the issue is changing life expectancy or quality of life for these patients. He stressed the need for credentialed training programs and labeling that clarifies that cooled ablation is not a definitive procedure to eliminate VT or an alternative to ICD. Several panel members discussed the role for this device: whether it was an alternative for those with defibrillator or an adjunctive therapy. Dr. Vetrovec stressed the need for anticoagulation to prevent complications.

Panel Response to FDA Questions

The panel agreed that the data presented permitted assessment of the safety and effectiveness of the device and that the inclusion and exclusion criteria were generally appropriate for evaluation. Panel members agreed that the randomized data were sufficient to evaluate effectiveness without the crossover cohort, with some suggesting the crossover be left out altogether as unnecessary and others saying the pooled data were necessary to evaluate safety. The panel would have preferred the appropriate control to be a standard ablation system but agreed that having patients act as their own control was appropriate. The labeling should present trial data, including criteria for acute and chronic success and VT density, with chronic success defined as a lack of VT episodes. Because of insufficient numbers in the control group and an inappropriate time domain for fair mortality evaluation, the panel suggested giving the procedural mortality rate and stating there is no evidence to suggest long-term procedural mortality.

The panel thought that the clinical study design of the device did not adequately demonstrate its use as a first-line therapy for the treatment of VT in the trial's patient population. Labeling should be revised to read "The device has proven safe and effective in decreasing VT in a group of patients defined as follows: the majority had ischemic heart disease, were refractory to drug therapy, and had ICDs. This therapy maybe of benefit as an adjunct for the management of VT." The panel recommended deleting the contraindication to heparin and adding a warning on the risk of thrombus without appropriate anti-coagulation therapy. The catheter statements and warnings should be the same or similar to those on the Curtis Webber. The panel recommended putting the caution statements on impedance cut-off settings and on displayed temperature readings directly on the device itself, using the longer (b) version. Members recommended adding the individualization of treatment section the FDA had proposed. They recommended that sponsors work with the Agency to accurately characterize the procedure's risk and to revise the wording on invasiveness and likelihood of procedure-related mortality. Physician training requirements should be indicated in the labeling, and issues involving echocardiography, heparin use, and anticoagulation therapy should be discussed in the patient information section. The panel thought the data presented do not adequately demonstrate the safety and effectiveness of the device as labeled and recommended a postmarked study to look at safety to obtain a bigger denominator and to provide procedural morbidity and acute mortality data through long-term surveillance on the original cohort. The company was encouraged to perform studies on the applicability of the device on subgroups for first-line use and to study cold versus regular ablation.

OPEN PUBLIC HEARING

There were. no requests to speak

Executive Secretary John Stuhlmuller read the voting options to the panel. Dr. Tracy moved that the device be recommended to the FDA as approvable with the following conditions: 1) The indication section should-be modified to read that the device is an adjunct in the treatment of tachycardia. 2) Statements on death, low risk, and patient information section on risks and benefits should be amended. 3) The individualization of treatment section should be amended as suggested to include issues involving echocardiography, heparin use, and anticoagulation therapy issues. 4) A postmarket surveillance of the original cohort and other patients treated with the device should study long-term adverse events and mortality, with the number studied to be determined later. The motion was seconded and unanimously approved.

CLINICAL STUDY DESIGN ISSUES FOR VT ABLATION

Megan Moynahan, FDA biomechanical engineer, began the discussion of clinical study design issues.

On randomized study designs, the panel recommended that randomization does not have to be either to ablation or to drug therapy but depends upon the inclusion criteria. Inclusion criteria determine who the control is; some subgroups may require different first-line therapies.

Concerning outcome measures, the panel suggested that acute efficacy (procedural success) should be tracked, but it is a poor prognosticator of clinical outcome and is therefore not a primary endpoint in many cases. For other indications, acute efficacy could be defined in ways other than the preceding PMA. In defining long-term success, the number of VT episodes in the

follow-up period is important. The absence of VT episodes, however desirable, is not a realistic criterion. No crossover between patient groups should be allowed. For more structurally normal hearts, any recurrence is bad; therefore, recurrence should be defined as well. One year is an appropriate follow-up period to collect complication data, with three to six months appropriate for arrhythmia and several months for aortic valves.

On questions concerning drug regimen, the panel discussed the dilemma that ifa condition is refractory to drug therapy, the investigators must offer a better alternative, making it difficult then to have patients agree to possible randomization to drug therapy. For VT ablation studies, it was recommended that patients not be drug refractory. With this type ofpopu!ation, crossover should be allowed only if follow-up is complete or alternative circumstances have been defined in advance; for example, if crossover is linked with density of recurrence. Crossover could be allowed in cases of drug failure such as inability to tolerate a drug altogether.

In general comments about randomized trials, Dr. Simmons commented that he was very unenthusiastic about randomized trials of the sort discussed in the day's session because randomization to drug therapy can be simply inappropriate. The possibility of randomizing and comparing one device to another in an equivalence study was discussed, but it was noted that companies are not allowed to compare one investigational device to another. The panel thought that proportional randomization faci litates study entry if patients are kept in the control group without possibility of crossover, but its benefit is mainly in facilitating recruitment. Less refractory groups produce better odds of success. The mortality endpoint is not important except to show that device use does not increase mortality.

In discussing non-randomized study designs, the panel found it difficult to define an appropriate baseline period. Members suggested defining density and having a minimum density for enrollment or using a timeframe, depending on the inclusion criteria. On the relevance and definition of acute efficacy, they commented that acute success in a life-threatening VT situation is only an observation, not an endpoint. For long-term efficacy, a "clinically meaningful improvement" in frequency of VT episodes should be validated by a quality of life measure, using any of the validated questionnaires or battery of measures. Any VT should be counted as a recurrence because of the difficulty of distinguishing between targeted and untargeted VT. The panel thought it inappropriate to compare the device's complication rate to drug-related complications.

The panel suggested assessing safety using historical control data on off-label ablation. The PMA just discussed was cited as a starting point. It was noted that the numbers on drug therapy in the published literature are somewhat optimistic. To measure clinical change, the panel suggested comparing the number of VT episodes during the baseline period to the follow-up period using ICD interrogation to get an idea of density, although the type of VT may be unclear because of changes in drug management. Event monitoring is also a useful method, but the panel thought ECGS from hospital visits were a problematic method and self-reporting was inaccurate. The same assessment method should be used pre- and post-ablation.

Genera! comments on non-randomized studies included the difference in ease of establishing effectiveness for scar-related VT versus idiopathic VT, with establishing effectiveness harder in the former and relatively easy in the latter group. Inclusion criteria would

have a domino effect on the study. It was noted that the choice of study design in relation to sponsor claim is tied to the ultimate prognosis of VT and what the investigator intends to accomplish. For a VT with bad prognosis, a large and long study would be necessary to impact mortality. A better prognosis could use a different model. To claim the device can be used as a first-line treatment for VT, a sponsor would need massive numbers and face ethical problems in proving the mortal it y impact. The panel agreed that mortality must be tracked but will be high regardless of device in the more malignant group. Rather than designing the study to make mortality a driving factor, investigators can collect mortality appropriate y and report it. It can be an endpoint or a risk factor, depending on the subgroup studied, for example, idiopathic VT versus structural heart disease VT. Inclusion criteria should be specified carefully and narrowly, and VT criteria t y pesshould be clearly and separately analyzed.

The meeting was adjourned at 5:00 p.m.

I certify that I attended the Open Session of the Circulatory Systems Devices Panel Meeting on July21, 1998, and that this summary accurately reflects what transpired.

John E. Stuhlmuller, M.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Tony W. Simmons, M.D.
Acting Chairman

Executive Summary prepared by

Aileen M. Moodie
9821 Hollow Glen PI.
Silver Spring, MD 20910
301-587-9722

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FOOD AND DRUG ADMINISTRATION

Thomas J. Callahan' Ph.D. .
Daniel Spyker, Ph. D., M.D.
Jennifer Goode

Stuart Portnoy

OPEN SESSION

Panel Chairperson Dr. Anne B. Curtis opened the session at 8:10 a.m. Panel Executive Secretary Dr. John Stuhlmuller read the conflict of interest statement and reported that matters concerning Drs. Aziz, Curtis, Simmons, and Vetrovec had been considered and waivers allowing their full participation had been granted. Dr. Curtis asked panel members to introduce themselves.

OPEN PUBLIC HEARING

Dr. Stuhlmuller noted correspondence from Boston Scientific Corporation and Cardima, Inc., which would be discussed during the deliberations. There were no requests to speak.

OPEN COMMITTEE DISCUSSION

FDA Presentation

Jennifer Goode noted that the Food and Drug Administration is developing guidance for industry on clinical trial design for catheter ablation systems intended to treat atrial flutter and atrial fibrillation and is seeking guidance from the panel on various questions. She defined typical atria] flutter (AFL) and gave its clinical profile and summarized the appropriate ACC/AHA 1995 Guidelines concerning ablation. She asked for comments on the role of drug therapy in clinical study design in terms of relative risk and assessment of ablation success. She discussed success rates, major complication rates, and length of follow-up as described in the medical literature. The FDA was seeking panel guidance on length of follow-up, inclusion criteria, and primary and secondary endpoints.

Panel Discussion

Atrial Flutter. On questions concerning clinical trial design, the panel discussed the difficulty of designing a study in the absence of an FDA-approved catheter with an indication for ATF use as the comparison. The panel consensus was that there was sufficient information in the literature to create objective performance criteria (OPCs) based on historical controls for new catheters to meet, although Dr. Tracy argued for taking currently used catheters and comparing them to historical controls to obtain a comparison standard. The panel suggested an 80°A minimum and 90°/0 desirable acute success rate, with a recurrence rate of 5°/0 minimum to 20°/0 maximum. Patients would serve as their own controls, with the primary endpoint being no recurrent flutter. The sponsor could provide a six-month to one-year registry for each device wanting approval for a new indication.

For patient selection criteria, the panel recommended that patients with any flutter, regardless of previous drug failure, were reasonable candidates, and that patients not previously treated with antiarrhythmic medication could be included in the study. Members suggested two or more reported symptoms of AFL per year as the minimum definition for inclusion, with one or more documented episode of AFL. The panel suggested that patients who have previously failed ablation therapy could be included in clinical study of an investigation ablation system but that data should be analyzed separately.

On endpoints, the panel recommended defining acute success as hi-directional conduction block. Chronic success was defined as the patient being arrhythmia-free for a minimum of six months, with an even longer mean. Success during follow-up was defined as absence of flutter;

there is no definition of partial success because even one recurrence of flutter should be counted a failure. Repeat ablations can be offered but should be counted as failures. In considering atrial fibrillation (AFib) "secondary to AFL," the panel members objected to the phraseology, saying that AFib is often a totally separate issue rather than a procedure failure, and a separate outcome measure, not an adverse event or chronic failure. Members noted that it is important to document beforehand if the patient has any AFib. To obtain a clean study, one exclusion criterion should be patients requiring chronic anti-arrhythmia drugs for AFib.

Atrial Fibrillation (AFib). Stuart Portnoy, FDA Biomedical Engineer, defined AFib and gave its clinical profile, noting that AFib patients have an increased risk of stroke. He discussed initial treatment of AFib and AFib therapeutic interventions, saying that catheter ablation of AFib involves linear lesions made with a catheter-based MAZE procedure using prescribed right and left atrial lesion sets. He noted that the medical literature suggests that right and left atrial lesions are more effective than right atrial lesions alone, but there is a potential for increased risk of throboembolic complications during left-heart catheterizations, and he presented preliminary clinical data from literature studies.

Dr. Stuhlmuller read comments from Boston Scientific Corporation asking the panel to consider four questions regarding the basis for estimated sample sizes for clinical trials, the appropriate method for analyzing safety data and the relationship between a complication and the procedure or investigational device, the definition of major and minor adverse events, and determination of safety and efficacy for combined system approaches to cure AFL and AFib. He

noted comments from Cardima and a statement from the North American Society of Pacing and Electrophysiology (NASPE), which were incorporated throughout the following discussion.

In discussing the FDA questions on atrial fibrillation, the panel noted that AFib is significantly different from AFL because much less literature exists on AFib and AFib has significant complications. No OPCS exist that are a gold standard for catheter or surgical options. Major complication rates from other arrhythmias do not apply because the AFib rates will be greater, and there are no benchmarks on the risk of stroke.

In considering clinical trial design questions relating to AFib, Dr. Stuhlmuller read the Cardima comment that a randomized concurrently controlled study should not be excluded but other viable designs, such as a single-arm nonrandornized trial with patients serving as their own control, should be explored. The panel consensus was also to recommend a single-arm, nonrandomized trial with the patient serving as his own control. They thought it unlikely that factors such as the evolving technique of A Fib ablation and new catheter designs would affect this choice of control. The panel suggested allowing paroxysmal and persistent but not chronic AFib patients in the study and using a quality of life endpoint for effectiveness. The members recommended that patients with large atria not be excluded a priori but could be limited.

In discussing how many episodes a patient must experience to be included in the study, the panel suggested obtaining data from the National Institutes of Health (NIH) Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial mentioned by NASPE. NASPE's comments on the absence of data to describe the recurrence patterns of abnormal atrial fibrillation either pre- or post-ablation were noted. Dr. Stuhlmuller read

Cardima's comments that establishment of baseline data should be a prerequisite. Cardima suggested that one-month data might be adequate for most patients to enter the trial, with three months' observation with one or more episode per month for low-frequency patients. There was no panel consensus on how long the baseline observation period should be. One suggestion was that two or more episodes documented over three months on stable drug therapy might provide some prospective baseline observation period, but the panel saw pros and cons of prospective and retrospective observation. The panel suggested that the FDA might want more industry input on this topic. The panel wanted monitoring of some sort involving paper documentation during the baseline period rather than just reported symptoms.

On patient selection criteria, the panel agreed that all patients who are in the study should have tried drug therapy and failed at least one drug. It was suggested that patients should fail two antiarrhythmic drugs or could not tolerate or failed amiodarone. It was noted that different types of AFib ablation might have different inclusion and exclusion criteria. On labeling, it was suggested that indications should be broad and not specify the type of AFib but give study information in the clinical trials section unless the catheter is specific for treatment of focal AFib. Data on persistent AFib should be provided.

In discussing endpoint questions, Dr. Stuhlmuller read the Cardima response that there is inadequate evidence to show that non-inducibility of AFib postablation is an appropriate indicator. The panel consensus was that no one knows what the correct endpoint is, nor do they know what acute noninducibility of fibrillation indicates. The panel thought that the gold standard is probably whether patients suffer symptomatic recurrences, but there are no answers in

the literature about when to have lab tests performed. In determining chronic success, the panel thought that the absence of AFib for the first X months would be a good indication and 75°A decrease or some similar, very significant decrease in frequency of symptomatic episodes over Y months may also be important. Specifying the Xs and Ys was too difficult because no data exist. The panel did not like using increased time to first recurrence of AFib as an endpoint. Members agreed that a blanking period after the procedure for a month or so is important.

While the measurement of acute success is difficult, the panel thought that the longer-terrn result is more important. It was agreed that putting a patient back on antiarrhythmic drugs is a failure or at best a partial success. Complete success would be no recurrence; a recurrence on antiarrhythmic drugs would be a partial success; a recurrence on antiarrhythmic drugs but with fewer episodes would be hard to assess.

A follow-up period of one year after the initial blanking period was suggested as appropriate for evaluating recurrences of arrhythmias in assessing chronic performance of the investigational ablation system. Data should be recorded during the blanking period but not considered as success or failure. The panel recommended that the patient should go home with a loop monitor and have some degree of Helter monitoring or trans-telephonic monitoring during the year. TEE should be performed on the left heart to assess the stroke risk.

On therapeutic approach questions, the panel thought that the risks between right and left heart treatment are inherently different and use on the right side does not predict left-side performance. One member suggested that animal data on the amount of thrombus on a new catheter system might be useful, although there was disagreement on this point.

On conducting a staged anatomical approach, one suggestion was that an initial feasibility study assess device performance on the right side, followed by a clinical trial on both right and left sides. Members noted that a right-side procedure may provide palliative relief by decreasing density of attacks, but both sides must eventually be ablated to cure.

The panel agreed that the optimal lesion set for treatment of AFib is unknown and suggested that it might be good to have more than one prescribed lesion set. A feasibility study on lesion sets will not provide long-term data but will provide some safety data.

Dr. Callahan thanked the participants on behalf of the FDA, and Dr. Curtis adjourned the meeting at 12:40 p.m.

I certify that I attended the Open Session of the Circulatory System Devices Advisory Panel Meeting on July 22, 1998, and that this summary accurately reflects what transpired.

John E. Stuhlmuller, M.D.
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

Anne B. Curtis, M.D.
Chairperson

Summary minutes prepared by
Aileen M. Moodie
Editorial Consultant
9821 Hollow Glen P1.
Silver Spring, MD 20910
301-587-9722